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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Toshiro Ono

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John R Van Amsterdam
c/o Wolf Greenfield and Sacks P C
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

EXAMINER

CANELLA, KAREN A

ART UNIT

PAPER NUMBER

1643

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/559,013	Applicant(s) ONO ET AL.	
	Examiner Karen A. Canella	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 54,56,60,62,64,66,76,133,134 and 137 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) 54,56,60,64,76,133 and 137 is/are allowed.
- 6) ☐ Claim(s) 62,66 and 134 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

Art Unit: 1643

DETAILED ACTION

Claims 54, 55 and 133 have been amended. Claims 54, 56, 60, 62, 64, 66, 76, 133, 134 and 137 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim 134 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how claim 134 further limits the scope of the nucleic acids of claim 56. Claim 56 is drawn to fragments of SEQ ID NO:23 of at least 50 nucleotides. Claim 134 requires that the isolated nucleic acids encode a polypeptide, wherein the polypeptide or a fragment of the polypeptide bind an antibody. Because any polypeptide can bind to an antibody this characteristic does not serve to limit claim 134.

Claims 62, 66 and 134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 62 is drawn to an isolated expression vector comprising a nucleic acid molecule of claim 54 and a nucleic acid encoding a MHC molecule. Claim 66 is drawn to an isolated host cell transformed with the expression vector of claim 60 further comprising a nucleic acid encoding a MHC molecule. Claim 134 is drawn in part to an isolated nucleic acid molecule of claim 56 wherein said nucleic acid molecule encodes a polypeptide which binds a MHC receptor, or a fragment of said polypeptide which binds a MHC receptor. The specification teaches the treatment of diseases in a patient comprising the administration of an amount of an agent which enriches for complexes of MHC/HLA molecules and a cancer associated antigen or a fragment thereof (page 8, line 28 to page 9, line 3). Thus the specification contemplates the

Art Unit: 1643

induction of an immune response by increasing the presence of a cancer associated antigen expressed in the context of MHC/HLA. The specification is enabling for the use of the polynucleotides encoding the cancer antigens of the invention for the detection of expressed polynucleotides to detect cancers. However, the specification is not enabling for the immunotherapy of cancer for the reasons set forth below.

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, *Fundamental Immunology*, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). The specification has provided evidence that two T-cell clones are able to lyse tumor cells expressing an epitope of the claimed tumor rejection antigen precursors in vitro. Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (*Nature Medicine*, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that

Art Unit: 1643

the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion"). In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105) and the abstract of Algarra et al (International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Paul (ibid) states that the induction of tolerance is a mechanism by which tumor cells escape immune detection. The art recognizes that T-cell are subject to clonal deletion within the thymus of a host and that this mechanism eliminates t-cell which are reactive with self-antigens. The specification teaches that the polypeptide encoded by SEQ ID NO:2 is indeed a self antigen, rather than a mutated self antigen, as it is expressed on normal tissues as well as cancerous

Art Unit: 1643

tissues. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete or shed antigens. In the instant case, the antigens are known self antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regimens comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells. Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even though P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the isolation of two T-

Art Unit: 1643

cells which are specific for the instant antigen presented in the context of HLA-A24, it cannot be determined if this is a reliable indicator that in all patients, with any of the types of cancers listed on page 20, would have a T-cell available after thymic selection which would react with said antigen in the context of HLA-A24 or any other MHC molecule. Further, the presence of CTL which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis of target cells expressing a target tumor antigen in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

It is noted that generic "cancers" would not be expected to initiate or maintain the same growth kinetics. This is of importance with regard to the teachings of Paul (ibid) on tumor cell escape mechanisms which include rapid growth as a means to overwhelm a slower immune response, (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4) and deficient antigen processing by tumor cells. With regard to the antigen processing, it is unclear whether all patients having a cancer expressing the disclosed antigen would have T-cells which were specific from the disclosed antigen, as the art teaches that the presence of a small number of tumor cells or the presence of a large number of tumor cells gives rise to tolerance (Paul, page 1166, second column, lines 19-23 under the heading "Sneaking Through"). Based on this observation, it is reasonable to conclude that a small number of slow growing tumor cells would elicit tolerance, and a large number of rapidly growing tumor cells would also elicit tolerance in line with the bi-phasic response reported by Paul. Thus, it appears that the interaction of the tumor cells with the host can produce tolerance by means of clonal deletion within the thymus of said host. Furthermore, the relationships between the multitude of different tumor cells exhibiting said antigen to the host would be variable as different types of organs (neuroblastoma,

Art Unit: 1643

brain, colorectal, gastric, head-and neck, lung, prostate, breast, thyroid, bladder, kidney, leukemia, etc) and different histological types of neoplasms (carcinoma, squamous cell, mesothelial, neuroepithelial, sarcoma, leukemia, etc) all present said disclose antigen. It is further noted that the claims are broadly drawn to a method of treatment of a cellular abnormality. When given the broadest reasonable interpretation, this read on diseases and conditions other than cancer. The specification does not disclose or suggest methods of treatment for diseases other than cancers.

Further, the claims are drawn to combinations of nucleic acids yielding non-specific peptide sequences. It is noted that Burch WO 03/084467 teaches that although putative epitopes can be predicted using a computer to scan the sequence of the gene (antigen) for amino acid sequences that contain a "motif" or a defined pattern of amino acid residues associated with a particular MHC (HLA) allele and the "predicted" epitope sequences can then be synthesized and tested, the vast majority of epitope sequences which have been "predicted" to be immunogenic failed to be immunogenic in standard assays. Thus one of skill in the art would be forced into undue experimentation to find test all the epitopes encompassed by the instant claims..

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering tumor antigen precursors or tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor in situ, and it cannot be predicted based on the isolation of two T-cell clones specific for said antigen from a single patient having melanoma, that the group of patients having the cancers as indicated on page 20, would all have a T-cell repertoire that would include a T-cell specific for the disclosed self antigen. Without said T-cell in the repertoire of the host, presentation of said antigen by an antigen-presenting cell after vaccination with the disclosed polypeptide or cell expressing said disclosed polypeptide would not evoke a T-cell response, as the appropriate T-cell would not be available in the periphery to be activated by said antigen-presenting cell. Thus, without a demonstration that the administration of the claimed polypeptides or cells expressing said polypeptides overcomes immunosuppression of the host, the rapid growth of the target tumor cells, failure to access the tumor because of the stromal barrier and tolerance induction in

Art Unit: 1643

the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of treatment.

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

4/28/2006


KARENA. CANELLA PH.D
PRIMARY EXAMINER